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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,603	01/09/2002	Nicholas Thomas	PA-9902	7928

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PATENT DEPARTMENT
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,603	THOMAS ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed December 17, 2003. Currently, claims 1-13, 15-17 are pending.

2. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims.

3. This action is made FINAL.

Priority

4. This application claims is a 371 of PCT/GB00/00807, filed March 9, 2000. The application also claims benefit of 9905807.5 filed March 12, 1999.

Drawings

5. The drawings are acceptable.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-4, 6-13, 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Beattie et al. (US Pat. 6,268,147, July 2001).

Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads

streaming past the detector window (col. 39, lines 5-10)(limitations of Claim 4). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of color coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined rations at different levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30). Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

Response to Arguments

The response traverses the rejection. The response asserts Beattie describes a method which requires hybridization of three molecules in tandem which are analyzed

by flow cytometry (page 8 of response filed October 19, 2004). The response asserts that in the instant invention "the nucleic acid samples being analyzed are labeled, and no separate, labeled stacking probe is needed for the flow cytometry detection to occur" (page 9 of response filed October 19, 2004). This argument has been reviewed but is not convincing because the claims are broadly drawn to methods which encompass the "labeled stacking probes" of Beattie. The claims are drawn to "comprising methods" and thus encompass additional elements. Specifically, the claims require providing nucleic acids from two sources as labeled probes wherein the nucleic aicds from each source is labeled with a distinct marker, forming pools comprising beads which are distinguishable, incubating and analyzing. As stated previously Beattie contemplates, "if dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)." The claims do not exclude the use of stacking probes, a third probe, for example. Thus, it is unclear how the claimed invention differs from the teachings of Beattie.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al. (US Pat. 6,268,147, July 2001) in view of Cocuzza et al. (US Pat. 5,484,701, January 1996).

Beattie et al. (herein referred to as Beattie) teaches a method of nucleic acid analysis using tandem hybridization on color-coded microspheres and flow cytometric detections (Example 18)(limitations of Claim 14). Beattie teaches that the stacking hybridization approach is applicable to "bead technology" where different capture probe sequences are tethered to microspheres which are distinguishable by any measurable (detectable) unique physical or chemical property associated with each bead, such as size, shape, mass, spectral profile, chemical reactivity, electronic properties, etc (col. 38, lines 35-43)(limitations of Claim 8-12, 16-17). Beattie teaches that the nucleic acid analyte is annealed with a labeled stacking probe of sequence and length designed to

bind to a unique position within the analyte nucleic acid (col. 38, lines 60-64). Beattie teaches that expressed sequence-specific stacking and capture probes may be used with RNA or cDNA analyte, the relative level of label bound to each color-coded bead will provide a gene expression (transcriptional profile)(limitations of Claims 2-3). As seen in Figure 15A and 15B, the target is labeled with a longer labeled stacking probe or a short labeled probe allele-specific or expressed sequence specific (limitations of Claim 6, 7). For genotyping and mutation analysis, allele specific capture probes are hybridized with genomic DNA or mixture of PCR products, preannealed with a mixture of stacking probes. The quantity of label associated with each color-coded bead is quantitatively determined using flow cytometry with spectral analysis of individual beads streaming past the detector window (col. 39, lines 5-10). Beattie teaches that the stacking probe must be labeled with a tag that is distinguishable from the spectral properties of color-coded beads. If dual labels are used (one used with a reference sample and another used with a test sample) the two samples are hybridized with a mixture of color-coded beads, and the relative binding of the two labels from the stacking probes to each color-coded bead will reveal the two transcriptional profiles (col. 39, lines 15-25)(limitations of Claim 13). Beattie teaches that for gene expression profiling, each expressed sequence is represented by a specific capture probe tethered to a color-coded bead, plus a labeled probe which hybridizes in tandem with the capture probe. The level of label bound to each color-coded bead reveals the transcriptional provide. The reference and test transcriptional profiles may be compared (col. 40, lines 10-15). Beattie teaches that a high degree of multiplexing is provided by the use of

color coded beads (col. 40, lines 22-25). Thousands of different color codes can be distinguished using several fluorescent dyes mixed together in defined rations at different levels, providing a large number of distinct spectral profiles (col. 40, lines 25-30). Beattie teaches that as long as the labels associated with the stacking probes are distinguishable from those of the "coded" beads, a wide variety of physical or chemical properties may be incorporated into microsphere to enable alternative bead-identifying detection schemes (col. 40, lines 30-35).

Beattie does not specifically teach immobilizing probes on beads using biotin and streptavidin-coated beads.

However Cocuzza teaches oligonucleotides may be immobilized on a bead using biotin /streptavidin-complexes. Coucuzza teaches that the biotin-avidin (streptavidin) system is a very useful analytical tool (col. 2, lines 5-8). The avidin and streptavidin form an exceptionally tight complex with biotin. Cocuzza teaches that the complexation is effectively an irreversible process 9col. 2, lines 23-25).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have immobilized the oligonucleotide probes of Beattie onto beads using the well known method of using biotin/streptavidin for immobilization taught by Cocuzza. The ordinary artisan would have been motivated to have immobilized polynucleotides using the biotin/streptavidin system for the expected benefit of tight complexes and east of use, as taught by Cocuzza.

Response to Arguments

The response traverses the rejection. The response asserts that "there is a fundamental difference between the current invention and that of Beattie." This argument has been reviewed but is not convincing because the claims are broadly encompass methods comprising the recited steps and do not exclude the use of hybridization of three nucleic acid molecules. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

9. No claims allowable over the art.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

a) Chandler et al. (US Pat. 5,981,180, November 1999) is directed to methods of using flow cytometry to distinguish various biomolecues in real time. Chandler does not specifically teaches the use of two labeled sources.

b) Kamb et al (WO 98/26098, June 1998) teaches a method for measuring relative amounts of nucleic acids in a complex mixture and retrieval of specific sequences. Kamb does not appear to teach pooled reagents which are distinguishable from the beads of any other pooled reagents by flow cytometry.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Patent Examiner
December 28, 2004